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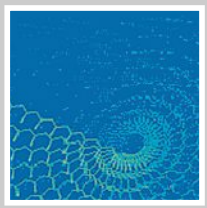

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Understanding Vesicle Origami

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Phospholipid vesicles are self-assembled bilayer structures surrounding an aqueous inner cavity. This cavity can take up drug molecules and such liposomes represent a well-advanced field of nanomedicine with several formulations translated into the clinics.[1] The field, however, seems stuck and particularly in tumor targeting no significant advances have been made in the past decade.[2] This is a clear sign that we do not understand the tools we are using and it is therefore vital to take a step back and study the fundamental biophysical properties of phospholipid vesicles. We decided to do this by probing the forces at play in liposome self-assembly using artificial phospholipids.

A typical drug delivery vesicle is in a liquid crystalline phase which leads to a spherical shape.[3] Compared to this, a vesicle in a gel phase possesses a much stiffer membrane and because of strain energy minimization, the membrane moves out-of-plane and forms facets, akin to the icosahedra of some viruses. Playing with the attractive and repulsive forces in a membrane, we can actively change the shape of a vesicle, leading to vesicle origami.

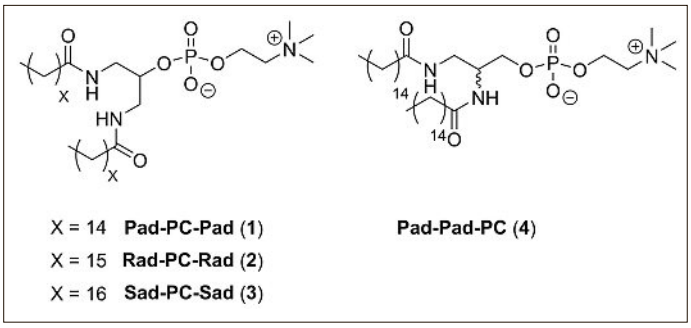

Fig. 1. Molecular structures of the class of 1,3-diamido phospholipids (**1**, **2** and **3**) and the 1,2-diamido phospholipid Pad-Pad-PC (**4**).

In the past years, we investigated different approaches to alter membrane properties, combining organic synthesis with monolayer and bilayer studies. A first motive leading to faceted vesicles are 1,3-diamido phospholipids (Fig. 1: **1**–**3**). Compared to natural *sn*-1,2 phospholipids, the acyl chains are spaced further apart, which leads to bilayer membrane leaflet interdigitation.[4,5] Cryogenic transmission electron tomograms reveal non-spherical vesicles of a developable form with overall zero Gaussian curvature (Fig. 2: A,C). The defect line at the intersection of the membrane faces renders the vesicle mechanoresponsive leading to a new concept in nanomedicine: targeting of atherosclerotic blood vessels through a physically triggered release mechanism.[6]

A second way to induce extreme vesicle faceting is to increase the attractive intermolecular forces with large hydrogen bond networks. Here, an optimized geometry is achieved with 1,2-diamido phospholipids (Fig. 1: **4**), forming stiff membranes in a subgel herringbone packing that cannot be bent in any direction. Forcing **4** to self-assemble into a closed 3D structure leads to a minimization of membrane intersections (edges) and a maximization of flat membrane faces, resolved in a cuboid structure (Fig. 2: B,D).[7]

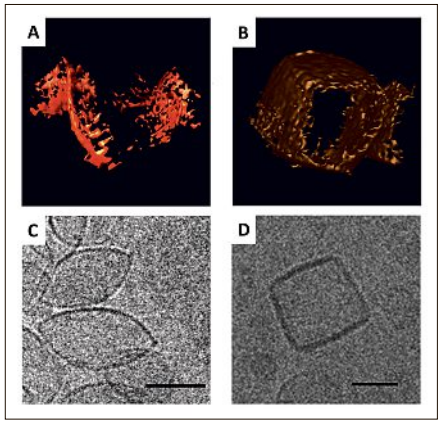

Fig. 2. A) Cryogenic transmission electron tomogram of faceted vesicles formulated with Pad-PC-Pad (**1**). B) Cryo transmission electron tomogram of Pad-Pad-PC (**4**) containing vesicles. C) and D) cryogenic transmission electron micrographs of Pad-PC-Pad (**1**) (C) and Pad-Pad-PC (**4**) containing vesicles. Scale bars are 50 nm wide.

Our approach to synthesize artificial phospholipids gives us the flexibility to optimize our existing drug delivery system for pharmaceutical applications. Combining the fundamental knowledge on membrane self-assembly from our diamido phospholipid studies[4] and research on the phospholipid substitution patterns[7] prompted us to synthesize the odd-numbered 1,3-diamido phospholipid Rad-PC-Rad (**2**).[5] Compared to Pad-PC-Pad (**1**) (T_m = 37 °C),[6] Rad-PC-Rad (**2**) shows an elevated main phase transition temperature of 45 °C and a processability that is lacking in Sad-PC-Sad (**3**).[5] These properties make Rad-PC-Rad (**2**) suitable for shear stress-triggered release of drug molecules in stenosed arteries, as a first-line treatment of myocardial infarction.

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